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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,046	04/17/2006	Toshikazu Nakamura	2006_0233A	8161

513 7590 08/19/2008

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
08/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,046	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,8-10,12-17,20,21 and 25-27* is/are pending in the application.

4a) Of the above claim(s) *1,4,5,8-10,13-17,20,21 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 4-5, 8-10, 12-17, 20-21, 25-27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-3, 6-7, 11, 18-19, and 22-23 have been cancelled.

Applicant's arguments filed 6/9/08 have been fully considered but they are not persuasive.

Claim 12 is under consideration by the examiner.

Election/Restrictions

Claims 1, 4-5, 8-10, 13-17, 20-21, and 24-27 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/21/07.

Claim Objections

Claim 12 is objected to because of the following informalities: Claim 12 appears to contain a grammatical error. It appears that the claim should recite either "formation in **a** skin ulcer" or "formation in skin ulcer**s**" rather than "formation in skin ulcer." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 12 has been substantively amended. Part (b) recites "a protein having at least 95% homology to SEQ ID NO: 1 and encodes a functional protein." The basis pointed to is not agreed with.

The specification does not contemplate, disclose, or define a "functional" protein. While applicant argues that this is intended to mean a protein with a particular HGF activity, the specification does not set forth this concept. (See parts (b), (d), and (e) with respect to this recitation.)

The specification does not contemplate or disclose a protein having at least 95% homology to SEQ ID NO: 1 (an amino acid sequence). While the specification does disclose at least 95% homology to SEQ ID NO: 2 (a nucleotide sequence), these are not equivalent concepts. For example, in a nucleotide sequence of 300 nucleotides this could permit the change of 15 nucleotides. The nucleotide changes could potentially change as many as 15 amino acids in the 100 amino acid sequence encoded.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 1, does not reasonably provide enablement for other mutations (insertions, substitutions, or deletions) in the first Kringle or elsewhere within human HGF. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a definition of a "functional protein." It is not considered to be limited to a protein with a particular HGF activity as proteins can have other functions (for example, binding ability (with or without a resulting activity) and antigenicity). The specification provides no guidance or enablement as to the structure or function of those proteins that would meet the limitation of functional and be operable in the claimed method.

In particular, part (a) recites "comprising **an** amino acid sequence **described** in SEQ ID NO: 1 of Sequence Listing." This recitation is interpreted to include subsequences of SEQ ID NO:1. It is not considered to be limited to a protein comprising the amino acid sequence of SEQ ID NO: 1. As such, the proteins embraced by this portion of the claim would be highly variable.

In particular, part (d) recites "hybridizing under highly stringent conditions to **a** nucleic acid of SEQ ID NO: 2 and encoding a functional protein." This recitation is interpreted to mean subsequences of SEQ ID NO: 2 and not the full length sequence. As such, the proteins embraced by this portion of the claim would be highly variable.

The specification discloses SEQ ID NO: 1 as being a mutated form of human HGF wherein five amino acids corresponding to amino acids 161-165 of SEQ ID NO: 3 (wild type human HGF) are deleted. (See pages 14 and 37 of the specification and SEQ ID NOS: 1 and 3.) The prior art (see at least Seki et al.) makes clear that the protein of SEQ ID NO: 1 is the result of a naturally occurring polymorphism. Seki et al. demonstrates that this form retains the same biological activity as the full length HGF of SEQ ID NO: 3. The specification does not disclose any other deletions or mutations in the first Kringle or elsewhere that would provide an active

HGF that could be used in the claimed method for promoting granulation formation. It is not considered to be so predictable that other mutations would result in an active protein based on the lack of information, guidance, and examples in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Toyoda et al. in view of Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), and Yoshida et al. (Journal of Investigative Dermatology), and either Morishita et al. (U.S. Patent No. 7.247,620) or Morishita et al. (WO 02/089854).

Toyoda et al. discloses that overexpression of HGF in transgenic mice promotes granulation. Increased presence of HGF protein is determined by using antibodies. Toyoda

discloses topical or local administration of HGF to skin wounds to promote healing and granulation formation. The reference specifically suggests using HGF to treat refractory skin ulcers from various diseases. See page 99, right column, last paragraph, as well as abstract; pages 96-97 and 100, section 3.5, and Figures 2 and 5. Toyada et al. does not disclose the HGF of SEQ ID NO: 1.

Seki et al. discloses the HGF of SEQ ID NO: 1. This naturally occurring variant has the same biological activities as the HGF retaining the five amino acids (SEQ ID NO: 3). The variant still binds antibodies to HGF. See at least abstract and pages 323 and 325-326.

Nakamura et al. (U.S. Patent No. 5,342,831) discloses using HGF to treat skin ulcers (dermoulcers). Methods of administration, formulations, and dosages are disclosed. See at least column 2, lines 50-68, and column 5, lines 50-63.

Nakamura et al. (EP 461,560 A1) discloses the HGF of SEQ ID NO: 1. This naturally occurring variant has the same biological activities as the HGF retaining the five amino acids (SEQ ID NO: 3). See at least column 20, claims, and Figure 15.

Yoshida et al. discloses that inhibiting the action of HGF protein by using antibodies can suppress or inhibit granulation tissue formation. See at least abstract.

Morishita et al. (U.S. Patent No. 7,247,620) discloses treating diabetic skin ulcers by topical administration of the HGF gene to promote granulation. There is increased presence of HGF protein in the healing wound. (See at least abstract, claims, and column 3, lines 5-20; columns, 9-10, particularly column 10, lines 1-5 and 41-45; and columns 17-18.) Morishita et al. (WO 02/089,854) is the PCT from which the '620 patent originated and has an equivalent disclosure.

It would have been obvious to substitute the HGF variant of SEQ ID NO: 1 as taught by Seki et al. and Nakamura et al. (EP 461,560 A1) to treat diabetic skin ulcers as suggested by Moroshita et al., Nakamura et al. (U.S. Patent NO. 5,342,831) and Toyoda et al. With respect to Toyada et al., one of ordinary skill in the art would have appreciated that refractory ulcers include diabetic skin ulcers. This would have been a known complication of diabetes. Morishita et al. specifically disclose treating diabetic skin ulcers. One would have been motivated to do so as Toyoda et al. and Moroshita et al. both disclose that HGF protein promotes granulation and Yoshida et al. discloses that inhibiting the action of HGF protein by using antibodies can suppress or inhibit granulation tissue formation. Based on the teachings of Nakamura et al. ('560) and Seki et al., one of ordinary skill in the art would have expected the HGF variant of SEQ ID NO: 1 to have this biological activity.

With respect to Morishita et al. (U.S. Patent No. 7,247,620), applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Applicant's argues that the prior art did not applied did not specifically disclose diabetic skin ulcers. The art applied above addresses this point.

Applicant provides an FDA draft document concerning drug development in wound healing. The standards required for FDA approval of a drug to treat a particular condition do not correspond to the requirements to establish obviousness or patentability. The prior art applied

discloses an expectation that HGF would be successful in treating skin ulcers resulting from diabetes.

Applicant argues that Toyoda et al. teaches away by statements that HGF may not have a direct effect. The claims do not require a direct effect or mechanism and applicant's specification does not establish that those results were due to a direct effect of HGF.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (571)272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa